201-16141

Lisa Medley/DC/USEPA/US
12/29/2005 09:42 AM

To NCIC HPV@EPA
cc
bcc
Subject Fw: Test Plan and Robust Study Summaries

Lisa Medley
OPPT/OSWER Docket - EPA HQ Docket Center
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----- Forwarded by Lisa Medley/DC/USEPA/US on 12/29/2005 09:42 AM -----

Sandi MURPHY <sandi.murphy@arkemagroup.com>
12/23/2005 01:13 PM

To NCIC OPPT@EPA, Rtk Chem@EPA
cc
Subject Test Plan and Robust Study Summaries

Attached please find the test plan and currently available robust study summaries for Tetradecyloxirane, (CAS# 7320-37-8, also called 1,2-epoxyhexadecane) which Arkema Inc volunteered to sponsor in the HPV program in a letter dated October 21, 2005. The test plan and robust study summaries will be updated as additional information becomes available.

If you have any questions please feel free to contact me. My contact information is listed below.

Thank you,

Sandi

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Test Plan 1-2-epoxyhexadecane.pdf Robust summaries tetradecyloxirane.pdf

Arkema Inc.

201-16141

Test Plan for:

Tetradecyloxirane [CASRN 7320-27-8]

Prepared for

U.S. Environmental Protection Agency
HPV Challenge Program
1200 Pennsylvania Avenue
Washington, DC 20460

Prepared by

Arkema Inc.
2000 Market Street
Philadelphia, PA 19103-3222

1 EXECUTIVE SUMMARY

IN 2005 Arkema Inc. volunteered to sponsor tetradecyloxirane (CAS#7320-38-7) also know as 1,2-epoxyhexadecane, in the US EPA High Production Volume (HPV) Challenge Program. This material was previously considered an orphan under the HPV program.

This report and test plan covers the physical property; environmental fate processes; and the ecological, mammalian, and genetic toxicity endpoints for tetradecyloxirane as appropriate for a chemical intermediate with controlled transport.

Existing Data

Data on physical properties, environmental fate, ecotoxicity, and mammalian and genetic toxicity were collected from available reports, published literature, and various standard compilations of physical property data. The collected data were reviewed for acceptability and entered into an International Uniform Chemical Information Database (IUCLID) dossier.

Ecotoxicity, mammalian toxicity, and genetic toxicity data were scored using the Klimisch et al. (1977) scoring system to assess data reliability. Data with scores of 1 or 2 were considered reliable and sufficient to assess an endpoint without supplementary data. Studies rated 4 were considered supplementary. Robust summaries were prepared for available reliable studies and relevant supplementary data and were entered into the IUCLID dossier.

Tetradecyloxirane is a metabolite of 1-hexadecene, which has been evaluated in the HPV Challenge Program as part of the as part of the higher olefins category. Some supplementary data for tetradecyloxicrane includes the assessment of 1-hexadecene.

Tetradecyloxirane is an isolated intermediate with controlled transport to a limited number second parties that use the chemical in a controlled way as an intermediate with a well-known technology. Repeat dose data up to 2 year studies in two species are available.

The proposed test plan is summarized in Table 1.

Table 1. Proposed Tests for Tetradecyloxirane

Endpoint	Testing Proposed	Rationale
Melting point	No	Adequate existing information
Boiling point	No	Adequate existing information
Density	No	Adequate existing information
Partition coefficient	No	Adequate existing information
Water solubility	No	Estimated using EPIWIN v3.12
Photodegradation	No	Estimated using EPIWIN v3.12
Transport between environmental compartments	No	Estimated using EPIWIN v3.12
Stability in water	Yes	
Biodegradation	No	Adequate existing information
Acute fish	No	Adequate existing information
Acute Daphnia	No	Adequate existing information
Toxicity to algae	Yes	
Acute toxicity	No	Adequate existing information
Repeated dose toxicity	No	Adequate existing information
Reproductive toxicity	No	Adequate existing information
Developmental toxicity	No	Adequate existing information
Genetic toxicity	No	Adequate existing information

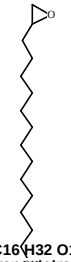
1.1 TEST SUBSTANCE

1.2 GENERAL SUBSTANCE INFORMATION

This material is used as a chemical intermediate with controlled transport. It is produced at a single location and shipped to a small number of second party users/locations where it is converted during processing to produce lubricants, surfactants, and additives for functional fluids for machinery, vehicles, and equipment. Any exposure potential would be limited to an industrial occupational setting. Tetradecyloxirane is an irritating material and a sensitizer.

Precautions are taken in manufacturing and processing to prevent contact. It is consumed and converted during processing. The products produced from the tetradecyloxirane are further diluted and used in formulations. There is no to very low potential for exposure to the tetradecyloxirane outside industrial occupational settings.

Table 2. General Substance Information

Compound	CAS No.	Molecular Formula	Molecular Weight (g/mol)	Estimated Purity of Named Substance	Structural Diagram
Tetradecyloxirane	7320-37-8	$C_{16}H_{32}O$	240.42	98%	 MolWt: 240.43 C16H32 O1 007320-37-8 Oxirane, tetradecyl-

1.3 REACTIVITY

Epoxides contain 3 membered carbon-carbon-oxygen rings which are reactive, due to the strain on the ring. Nucleophilic attack breaks a carbon-oxygen bond, opening the ring and relieving the strain. Generally, the result is the formation of a substituted alcohol; if the nucleophile is water, then diols or glycols are formed. Weak nucleophiles such as water require acid catalysts for the reaction to occur. Under acidic conditions, the nucleophile preferentially attacks the more substituted carbon in the ring, resulting in the formation of the less substituted alcohol. Under basic conditions, the nucleophile attacks the least hindered carbon in the ring and results in the formation of the more substituted alcohol. In living systems the enzyme epoxide hydrolase converts epoxides to trans-dihydrodiols. Based on these properties, this high molecular weight epoxide is stable under normal storage and handling conditions. Contact with acids, bases, or oxidizers can result in a low energy release.

1.4 DISCUSSION OF THE ADEQUACY OF THE EXISTING DATA

Arkema has reviewed the existing data set and feels that the existing data are adequate to characterize several of the aquatic and health effects of tetradecyloxirane for the purposes of the EPA HPV Challenge Program. Table 1 indicates where additional data are proposed to be developed.

2 PHYSICAL PROPERTY DATA

For tetradecyloxirane, data on physical properties were collected from reports, published literature, and various standard compilations of physical property data. The collected data were

reviewed for acceptability and entered into an International Uniform Chemical Information Database (IUCLID) dossier. Existing physical property data are summarized in Table 3 below.

Table 3. Physical Property Data for Tetradecyloxirane

Endpoint	Value	Source(s)
Melting Point	21°C(1)	The Dictionary of Substances and Their Effects (DOSE, 3rd Electronic Edition) 2005
Boiling Point	270 - 275 °C	Safety and Toxicity Data prepared for 1,2-epoxyhexadecane by Tracor Jitco July 26, 1978.
Density (g/cm^3)	0.85 @ 20 °C	The Dictionary of Substances and Their Effects (DOSE, 3rd Electronic Edition) 2005
Vapor Pressure	ca. 0.00285 hPa @ 25 °C	EPISuite v3.12 (MPBPWIN V. 1.41)
Partition Coefficient (log P_{ow})	ca. 6.76 @ 25 °C	EPISuite v3.12 (KOWWIN v1.67)
Water solubility	0.045 mg/L @ 25 °C	EPISuite v3.12 (WSKOW v1.41)
	0.0006 mg/L	Wood, 1982

Existing physical property data are considered adequate; therefore, no additional testing is proposed.

3 ENVIRONMENTAL FATE DATA

3.1 PHOTODEGRADATION

The Atmospheric Oxidation Program for Microsoft Windows (EPISuite v 3.12, AOPWIN v1.91) was used to estimate the rate constant for the atmospheric, gas-phase reaction between photochemically produced hydroxyl radicals and organic chemicals. These rate constants were used to calculate atmospheric half-lives based upon average atmospheric concentrations of hydroxyl radicals and ozone. The results are presented below and indicate that there is a moderate reaction rate and it will not be persistent in air.

Hydroxyl Radicals Reaction:

OVERALL OH Rate Constant =	18.7709 E-12 cm3/molecule-sec
Half-Life =	0.570 Days (12-hr day; 1.5E6 OH/cm3)
Half-Life =	6.838 Hrs

3.2 ENVIRONMENTAL TRANSPORT AND DISTRIBUTION (FUGACITY)

Fugacity modeling was performed using EPISuite v3.12. The results are listed below:

Level III Fugacity Model:

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	0.531	13.7	1000
Water	4.42	360	1000

Soil	31.2	720	1000
Sediment	63.8	3.24e+003	0

Persistence Time: 1.11e+003 hr

Based on this model the material is expected to partition primarily to soil and sediment.

3.3 BIODEGRADATION

Aerobic degradation was 26% after 20 days, so the material is inherently biodegradable. No testing is proposed. (Waggy, G.T., 1992).

3.4 STABILITY IN WATER (HYDROLYSIS)

There are no rate data related to the stability in water. Epoxides have the potential to undergo hydrolysis. Experience has shown that tetradecyloxirane is stable in water at neutral pH and room temperature, but will hydrolyze to form the glycol in acid solutions. Hydrolysis testing is proposed.

4 ECOTOXICITY DATA

Ecotoxicity data were collected from reports and published literature. The collected data were reviewed for acceptability and entered into an International Uniform Chemical Information Database (IUCLID) dossier.

4.1 ACUTE TOXICITY TO FISH

Data in the literature indicates that the LC50 is greater than the limit of solubility. (Deneer et al., 1988) Modeling makes the same prediction. No further testing is proposed.

4.2 ACUTE TOXICITY, AQUATIC INVERTEBRATES (DAPHNIA)

The EC50 for Daphnia magna is reported to be 1.25 mg/l. These data are adequate. No further testing is proposed. (Waggy, GT, 1992)

4.3 TOXICITY TO AQUATIC PLANTS (E.G., ALGAE)

No data on the toxicity to algae are available. Testing for algal toxicity is proposed.

5 MAMMALIAN TOXICITY

Based on animal studies, tetradecyloxirane had low acute oral and dermal toxicity, was slightly irritating to eyes, severely irritating to skin, and caused skin sensitization. It was not mutagenic when tested in bacteria, but elicited chromosomal effects to some types of cells in culture, and was negative in others. Histopathological findings in subchronic dermal studies (13 week duration) were identified in the skin but not in tissues remote from the site of application. Long term dermal exposure resulted in the development of skin tumors in mice but not rats.

5.1 ACUTE TOXICITY

The rat oral LD50 is greater than 5000 mg/kg. The rat dermal LD50 is greater than 2000 mg/kg. Clinical signs were noted in both studies during the observation period but no significant findings were noted at gross necropsy. (Springborn, 1996, 1996a) No further testing is proposed.

5.2 IRRITATION AND SENSITIZATION

Results of animal studies showed moderate (Myers and Christopher, 1992) to severe skin irritation (Springborn, 1996b). Some signs of irritation persisted up to the observation recorded on day 10 after dosing. All animals had recovered by the study termination at day 14. Minor transient conjunctival irritation was noted after application of 0.1 ml to rabbit eyes. All animals recovered completely by day 7. (Myers and Christopher, 1992; Springborn, 1996c)

Tetradecyloxirane was tested to assess the dermal sensitization potential (delayed contact hypersensitivity) in Hartley-derived albino guinea pigs when administered by multiple topical applications. Based on the results of this study, this material is considered to be a contact sensitizer in guinea pigs. (Springborn, 1996d)

5.3 REPEATED DOSE TOXICITY

Although the final reports of the NTP studies have never been published, the data are available in the archive. The information below was extracted from the records in the archive. (NTP Unpublished Study C55538)

Subchronic studies:

NTP conducted a 13 week skin painting study in rats as a dose range finding study prior to conducting a chronic study. Ten animals per sex per dose were administered test material 5 days per week for 13 weeks. The applied doses were 0, 62.5,125, 250, 500, and 1000 mg/kg at concentrations of 0, 3.75, 7.5, 15. 30, 60% in acetone.

Clinical observations were limited to irritation at the lower doses. At 500 mg/kg, during weeks 3 - 8, exfoliation of stratum corneum and alopecia were reported. Some females were thin. At 1000 mg/kg, during weeks 1 - 3, rough coats and slight erythema were observed; during weeks 4 - 13, exfoliation of the stratum corneum was also reported. During weeks 5 - 13, dark urine, emaciation (primarily in females), alopecia, and sores in treated area were reported.

There were compound related lesions observed in this study. These lesions the skin (site of application) and were manifested in a variety of changes. These changes consisted of

hyperkeratosis, parakeratosis, acanthosis, necrosis of cells, and necrosis with varying degrees of inflammation. In more severe cases, mostly high dose and mid dose animals, there was ulceration of the skin accompanied with acute and chronic inflammation. In one case, high dose male, there were pyogenic granulomas deep in the dermis and muscle.

Microscopic findings were limited to the skin and site of application. Deep dermal abscesses, focal ulceration, inflammation were reported.

A similar skin painting study was conducted in mice. Applied doses were 0, 62.5, 125, 250, 500, and 1000 mg/kg using test concentrations of 0, 0.9, 1.875, 3.75, 7.5, and 15%.

Reduced body weights were observed in males at doses > 250 mg/kg, beginning in the fourth week , but the body weights recovered to near controls for all doses by end of the study. Mean body weights of females varied too widely for any meaningful relationship to treatment.

Clinical observations, males: Males in all dose groups had sores on their backs likely due to fighting. Dose related signs of skin irritation were also noted. At 250 mg/kg, during week 7 some males had thin appearance. At 500 mg/kg, during week 7 survivors appear thin. During weeks 7 -13, conditions of survivors improved. At 1000 mg/kg, during week 11, three males had sores on their dorsal area.

Clinical observations, females: Dose related signs of skin irritation were noted. At 250 mg/kg: During weeks 8-9, rough coats and thin appearance were reported. Conditions improved through the remainder of the study. At 500 mg/kg, in week 7, survivors appeared thin. Condition improved for the remainder of the study. At 1000 mg/kg from week 7, thin appearance and dermal effects were reported until the end of the study.

Mortality: 2m/3f @ 250; 4m/4f @ 500; 8m/4f @ 1000 mg/kg; most deaths occurred during weeks 6 - 8.

Microscopic findings: hyperkeratosis (minimal to moderate) in 14 mice, parakeratosis in 3 mice, and epithelial hyperplasia in 8 mice. Except for the tissue changes in the skin of treated mice, there were no tissue changes attributable to the effects of the test material in any of the treated mice examined.

Chronic Toxicity/Carcinogenicity:

NTP conducted a 2 year skin painting study in rats . Fifty animals per sex per dose were administered test material 5 days per week for 103 weeks. The applied doses were 0, 62.5 and 125 mg/kg in acetone with concentrations of 0, 3.75, 7.5% (adjusted based on body weight to allow for administration of 600 microliters).

The test material was a skin irritant and induced proliferative changes when applied topically. No consistent compound related reduction in body weight occurred in any of the treatment groups. Periodic weight fluctuations were attributed to problems with the automatic watering system. The Pathology Working Group which evaluated the study results concluded that 2-epoxyhexadecane in a two-year skin paint study did not produce any compound related neoplastic or systemic toxic lesions in F344 rats.

NTP conducted a similar 2 year skin painting study in mice . Fifty animals per sex per dose were administered test material 5 days per week for 103 weeks. The applied doses were 0, 62.5 and 125 mg/kg in acetone with concentrations adjusted based on body weight to allow for administration of 200 microliters.

All groups of male mice, including controls, had a high incidence of subcutaneous, mesenchymal neoplasms including malignant sarcoma, fibrosarcoma, neurofibrosarcoma, benign fibroma, with a combined incidence of 5 (10%), 8 (16%) and 13 (26%) in the control, low, and high dose groups. Only one fibrosarcoma was clearly identified as occurring at the application site. The tumors were all visible grossly.

There was a modest increase in the incidence of hepatocellular adenomas in all groups of male mice. The incidence of hepatocellular carcinoma was low in control male mice and average for treated animals.

The pathology working group concluded that 1,2-epoxyhexadecane in a two year skin painting study was associated with a dose-related increase in subcutaneous mesenchymal neoplasms in male B6C3F1 mice. A clear relationship between the location of the neoplasms and the area of skin exposure to the test compound cannnot be established from the data except for one tumor.

There were no other neoplastic or systemic toxic compound related effects in B6C3F1 mice. The pathology working group considered the modest increase in hepatocellular tumors in male mice not to be of biological significance.

These data are adequate to assess the repeated dose toxicity of tetradecyloxirane. No further testing is proposed.

5.4 REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

For materials such as tetradecyloxirane, with limited exposure potential, the guidelines allow for reduced testing if there is adequate information from repeated dose studies for hazard assessment.

No information on the potential reproductive or developmental toxicity of tetradecyloxirane was located. However, there were no adverse histopathological findings in the reproductive tracts of rats or mice exposed dermally for 13 weeks or 2 years.

In addition to meeting the condition for reduced testing, there is supplementary information relevant to the material indicating that it would not be expected to affect reproductive performance or development of offspring.

The supplementary indications come from the available data for the higher olefins and their metabolism. Tetradecyloxirane is a metabolite of hexadecene. Hexadecene has been evaluated in the HPV program as part of the higher alpha olefins category of materials.

In vivo, hexadecene is metabolized to 1,2-dihydroxyhexadecane through a tetradecyloxirane intermediate. The conversion of tetradecyloxirane to 1,2-dihydroxyhexadecane is dependent upon epoxide hydrolase. Based on the information from the alpha-olefins category, no reproductive or developmental effects are anticipated. Since tetradecyloxirane is the reactive metabolite, the evalaution of hexadecene is relevant since the ultimate metabolite is the same for both compounds. The materials tested in the alpha-olefins category did not elicit reproductive or developmental effects at doses up to 1000 mg/kg in rats.

In addition, there is information on higher mmolecular weight analogies and materials with higher degrees of epoxidation, eg, epoxidized oils. As in the case of the alpha-olefins, they did

not elicit any reproductive or developmental effects in rats at doses up to 1000 mg/kg. Based on the lack of effects in structurally similar materials of lower and higher molecular weight, and, degree of epoxidation, there is adequate information upon which to base a screening level hazard assessment for these endpoints.

Because the material is an intermediate with limited transport and supplementary data are available regarding reproductive and developmental effects, no further testing is proposed.

6 GENETIC TOXICITY

Data from various *in vitro* gene mutation and chromosomal aberration tests of tetradecyloxirane were obtained from company-sponsored studies or from the scientific literature. *In vitro* genetic toxicity data are summarized in Table 4.

Table 4. *In Vitro* Mutagenicity and Genotoxicity of Tin Tetrachloride

Endpoint	Results	Source
Bacterial reverse mutation assay (single strain and multiple strains)	Negative	Hengler, W.C., Slesinski, R.S. and Frank, F.R. (1984); Canter et al., 1986.
Mouse lymphoma assay	Positive	McGregor DB, et al., 1988.
Sister Chromatid Exchange Assay (Chinese hamster cells)	Negative	von der Hude et al., 1991, Slesinski, et al., 1984 Union Carbide Corporation, 1984

There are adequate data to assess genotoxicity. No further testing is proposed.

7 REFERENCES

Canter DA, et al. Comparative Mutagenicity of Aliphatic Epoxides in Salmonella. Mutat Res 172(2):105-138, 1986

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Dow Europe GMBH MSDS alpha-Olefin Epoxide C-16, 30/3/04
EPI Suite v3.12, US EPA
Hengler, W.C., Slesinski, R.S. and Frank, F.R. (1984). Alpha-Olefin Epoxide C-16 Salmonella/Microsome (Ames) bacterial mutagenicity assay.
McGregor DB, et al. Responses of the L5178Y TK+/TK- Mouse Lymphoma Cell Forward Mutation Assay: III. 72 Coded Chemicals. Environ Mol Mutagen 12(1):85-154, 1988.

Myers, R.C. and Christopher, S.M. (1992). .... cutaneous and ocular irritancy testing using the rabbit.
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Nycum, J.S. (1968). Single dose toxicity and irritation studies on Epoxides
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Slesinski, R.S. and Frank, F.R. (1984). a-Olefin Epoxide -16 in vitro Genotoxicity Studies: Sister Chromatid Echange Test.
SPRINGBORN ENVIRONMENTAL SCIENCES Acute Oral Toxicity Study in Rats with Vikolox 16, SLI STUDY NO. 3255.80, 19 August 1996.
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Union Carbide Corporation. Alpha-Olefin Epoxide C-16 Salmonella/Microsome (Ames) Bacterial Mutagenicity Assay With Cover Letter. TSCA 8(d) submission. TSCATS Microfiche No. 206602. 03/05/84.

von der Hude W, Carstensen S, Obe G, Structure-Activity Relationships Of Epoxides: Induction Of Sister-Chromatid Exchanges In Chinese Hamster V79 Cells, Mutat Res, 249: 55-70,1991.

Wood WP, Properties Of Alkyl-Epoxides - Table I With Cover Letter, US Environmental Protection Agency EPA/OTS DOC 40-8277016, NTIS/OTS0508875

201-16141

I U C L I D

Data Set

Existing Chemical	:	ID: 7320-37-8
CAS No.	:	7320-37-8
EINECS Name	:	tetradecyloxirane
EC No.	:	230-786-2
Molecular Formula	:	C16H32O

Producer related part

Company	:	Arkema Inc.
Creation date	:	20.12.2005

Substance related part

Company	:	Arkema Inc.
Creation date	:	20.12.2005
Status	:	
Memo	:	
Printing date	:	23.12.2005
Revision date	:	
Date of last update	:	23.12.2005
Number of pages	:	43
Chapter (profile)	:	Chapter: 1, 2, 3, 4, 5, 6, 7, 8, 10
Reliability (profile)	:	Reliability: without reliability, 1, 2, 3, 4
Flags (profile)	:	Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

1.0.1 APPLICANT AND COMPANY INFORMATION

Type	:	cooperating company
Name	:	Arkema Inc.
Contact person	:	Sandra Murphy
Date	:	20.12.2005
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Homepage	:	
Source	:	Arkema Inc. Philadelphia, PA USA
Flag	:	non confidential

22.12.2005

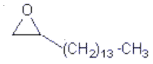
1.0.2 LOCATION OF PRODUCTION SITE, IMPORTER OR FORMULATOR

1.0.3 IDENTITY OF RECIPIENTS

1.0.4 DETAILS ON CATEGORY/TEMPLATE

1.1.0 SUBSTANCE IDENTIFICATION

IUPAC Name	:	
Smiles Code	:	O(C1CCCCCCCCCCCCC)C1
Molecular formula	:	C16-H32-O
Molecular weight	:	240.42
Petrol class	:	
Source	:	Arkema Inc. Philadelphia, PA USA
Attached document	:	EHD.bmp



21.12.2005

1.1.1 GENERAL SUBSTANCE INFORMATION

Purity type : typical for marketed substance
Substance type : organic
Physical status : liquid
Purity : ca. 98 % w/w
Colour : colorless
Odour : ether-like odour

Source : Arkema Inc. Philadelphia, PA USA
Reliability : Body weight data indicate a probable toxic effect at 10% and above in males and 20% and above in females.

22.12.2005

1.1.2 SPECTRA

Type of spectra : IR

Attached document : IR spectrum tetradecyloxirane.pdf
22.12.2005 (10)

1.2 SYNONYMS AND TRADENAMES

1,2-epoxyhexadecane

21.12.2005

Vikolox (R) 16

Source : Arkema Inc. Philadelphia, PA USA
22.12.2005

1.3 IMPURITIES

Purity : typical for marketed substance
CAS-No : 629-73-2
EC-No : 211-105-8
EINECS-Name : hexadec-1-ene
Molecular formula :
Value : ca. 2 % w/w

Source : Arkema Inc. Philadelphia, PA USA
21.12.2005

1.4 ADDITIVES

1.5 TOTAL QUANTITY

1.6.1 LABELLING

Symbols : Xn, N, ,

Nota : , ,
R-Phrases : (38) Irritating to skin
(40) Possible risks of irreversible effects
(51) Toxic to aquatic organisms
(53) May cause long-term adverse effects in the aquatic environment
S-Phrases :

21.12.2005 (3)

1.6.2 CLASSIFICATION

1.6.3 PACKAGING

1.7 USE PATTERN

Type of use : industrial
Category : Chemical industry: used in synthesis

Remark : Used primarily in the production of additives for functional fluids
Source : Arkema Inc. Philadelphia, PA USA
21.12.2005

1.7.1 DETAILED USE PATTERN

Industry category : 3 Chemical industry: chemicals used in synthesis
Use category : 33 Intermediates
Extra details on use category : Substance processed elsewhere
No extra details necessary
Emission scenario document : available
Product type/subgroup :
Tonnage for Application :
Year :
Fraction of tonnage for application :
Fraction of chemical in formulation :
Production : yes:
Formulation : :
Processing : yes: III Multi-purpose equipment
Private use :
Recovery :

Source : Arkema Inc. Philadelphia, PA USA
21.12.2005

1.7.2 METHODS OF MANUFACTURE

Origin of substance : Synthesis
Type : Production

Source : Arkema Inc. Philadelphia, PA USA
21.12.2005

1.8 REGULATORY MEASURES

1.8.1 OCCUPATIONAL EXPOSURE LIMIT VALUES

1.8.2 ACCEPTABLE RESIDUES LEVELS

1.8.3 WATER POLLUTION

1.8.4 MAJOR ACCIDENT HAZARDS

1.8.5 AIR POLLUTION

1.8.6 LISTINGS E.G. CHEMICAL INVENTORIES

1.9.1 DEGRADATION/TRANSFORMATION PRODUCTS

1.9.2 COMPONENTS

1.10 SOURCE OF EXPOSURE

1.11 ADDITIONAL REMARKS

1.12 LAST LITERATURE SEARCH

Type of search : Internal and External
Chapters covered : 3, 4, 5
Date of search : 07.12.2005

21.12.2005

1.13 REVIEWS

2.1 MELTING POINT

Value : 21 °C
Sublimation :
Method :
Year : 1999
GLP :
Test substance :

Source : Arkema Inc. Philadelphia, PA USA
Reliability : (2) valid with restrictions
22.12.2005 (21)

2.2 BOILING POINT

Value : = 270 - 275 °C at
Decomposition :
Method : other: micro, capillary visual
Year :
GLP :
Test substance :

Remark : Literature values 104 - 106 C at 0.2 mm Hg
Source : Arkema Inc. Philadelphia, PA USA
Reliability : (2) valid with restrictions
22.12.2005 (14)

2.3 DENSITY

Type : density
Value : .846 at 20 °C

Source : ATOFINA Chemicals Inc. Philadelphia
Reliability : (2) valid with restrictions
22.12.2005 (21)

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

Value : ca. .00285 hPa at 25 °C
Decomposition :
Method : other (calculated)
Year :
GLP : no
Test substance : no data

Result : Boiling Pt, Melting Pt, Vapor Pressure Estimations (MPBPWIN v1.41):

VP(mm Hg,25 deg C): 0.00214 (Modified Grain method
Source : Arkema Inc. Philadelphia, PA USA
Reliability : (2) valid with restrictions
22.12.2005 (7)

2.5 PARTITION COEFFICIENT

Partition coefficient	:	octanol-water
Log pow	:	ca. 6.76 at 25 °C
pH value	:	
Method	:	other (calculated)
Year	:	
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	KOWWIN Program (v1.67)
Result	:	WSKOW v1.41 Results ---------- Log Kow (estimated) : 6.76 Log Kow (experimental): not available from database Log Kow used by Water solubility estimates: 6.76 Equation Used to Make Water Sol estimate: Log S (mol/L) = 0.796 - 0.854 log Kow - 0.00728 MW + Correction (used when Melting Point NOT available) Correction(s): Value ---------- ----- No Applicable Correction Factors Log Water Solubility (in moles/L) : -6.724 Water Solubility at 25 deg C (mg/L): 0.045
Source	:	Arkema Inc. Philadelphia, PA USA
Reliability	:	(2) valid with restrictions

22.12.2005 (4)

2.6.1 SOLUBILITY IN DIFFERENT MEDIA

Solubility in	:	Water
Value	:	ca. .045 mg/l at 25 °C
pH value	:	
concentration	:	at °C
Temperature effects	:	
Examine different pol.	:	
pKa	:	at 25 °C
Description	:	
Stable	:	
Deg. product	:	
Method	:	other: estimate
Year	:	
GLP	:	
Test substance	:	
Source	:	Arkema Inc. Philadelphia, PA USA
Reliability	:	(2) valid with restrictions

22.12.2005 (4)

Solubility in	:	Water
Value	:	ca. .0006 mg/l at °C
pH value	:	
concentration	:	at °C
Temperature effects	:	

Examine different pol.	:	
pKa	:	at 25 °C
Description	:	
Stable	:	
Deg. product	:	
Method	:	other
Year	:	
GLP	:	
Test substance	:	

Method : Estimate based on structure
23.12.2005 (26)

2.6.2 SURFACE TENSION

2.7 FLASH POINT

Value	:	93 °C
Type	:	
Method	:	other: closed cup
Year	:	
GLP	:	
Test substance	:	

Source : Arkema Inc. Philadelphia, PA USA
Reliability : (2) valid with restrictions
22.12.2005 (21)

2.8 AUTO FLAMMABILITY

2.9 FLAMMABILITY

2.10 EXPLOSIVE PROPERTIES

2.11 OXIDIZING PROPERTIES

2.12 DISSOCIATION CONSTANT

2.13 VISCOSITY

2.14 ADDITIONAL REMARKS

3.1.1 PHOTODEGRADATION

3.1.2 STABILITY IN WATER

3.1.3 STABILITY IN SOIL

3.2.1 MONITORING DATA

3.2.2 FIELD STUDIES

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

Type : fugacity model level III
Media :
Air : % (Fugacity Model Level I)
Water : % (Fugacity Model Level I)
Soil : % (Fugacity Model Level I)
Biota : % (Fugacity Model Level II/III)
Soil : 31.2 % (Fugacity Model Level II/III)
Method : other: model
Year :

Result : Level III Fugacity Model:

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	0.531	13.7	1000
Water	4.42	360	1000
Soil	31.2	720	1000
Sediment	63.8	3.24e+003	0

Persistence Time: 1.11e+003 hr

EPI SUMMARY (v3.12)

Source : Arkema Inc. Philadelphia, PA USA
21.12.2005 (4)

3.3.2 DISTRIBUTION

3.4 MODE OF DEGRADATION IN ACTUAL USE

3.5 BIODEGRADATION

Type : aerobic
Inoculum :
Contact time :
Degradation : = 26 (±) % after 20 day(s)
Result :

Deg. product	:	
Method	:	
Year	:	
GLP	:	yes
Test substance	:	
Remark	:	Data provided by Dow.
Source	:	Arkema Inc. Philadelphia, PA USA
Reliability	:	(2) valid with restrictions

22.12.2005 (24)

Type	:	aerobic
Inoculum	:	
Deg. product	:	
Method	:	other: Modeled estimate
Year	:	
GLP	:	
Test substance	:	
Result	:	Probability of Rapid Biodegradation (BIOWIN v4.01): Linear Model : 0.3942 Non-Linear Model : 0.1201 Expert Survey Biodegradation Results: Ultimate Survey Model: 2.9575 (weeks) Primary Survey Model : 3.7602 (days) Readily Biodegradable Probability (MITI Model): Linear Model : 0.6733 Non-Linear Model : 0.766
Source	:	Arkema Inc. Philadelphia, PA USA

22.12.2005

3.6 BOD5, COD OR BOD5/COD RATIO

3.7 BIOACCUMULATION

3.8 ADDITIONAL REMARKS

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type : semistatic
Species : Lebistes reticulatus (Fish, fresh water)
Exposure period : 14 day(s)
Unit : µmol/l

Method : Five concentrations geometrically increaseing with a factor of 1,8 were tested for each material, exposing 10 fish to each concnetration. Actual concnetrations were measured at least four times after and four times before renewal . Concnetrations were deteremined using G-LC with an FID detector.
Result : For 1,2-epoxyhexadecane no LC50 could be determined. It is likely that the solubility of this compoundis too low to cause lethal effects.
Conclusion : LC50 value is greater than the limit of water solubility.
Reliability : (2) valid with restrictions
23.12.2005 (2)

Type : other: model estimate
Species :
Exposure period :
Unit : mg/l
LC50 : ca. .323 calculated
Method : other: ECOSAR V0.99
Year :
GLP :
Test substance :

Result : ECOSAR v0.99h Class(es) Found

Epoxides
Predicted Values:
Neutral Organic SAR: Fish,14-day LC50 0.023 mg/l*
(Baseline Toxicity)

Epoxides: Fish, 96-hr LC50 0.323 mg/l *
Epoxides: Fish, 14-day LC50 0.351 mg/l *

Note: * = asterisk designates: Chemical may not be soluble enough to measure this predicted effect.
Fish and daphnid acute toxicity log Kow cutoff: 5.0
MW cutoff: 1000
Source : Arkema Inc. Philadelphia, PA USA
22.12.2005 (4)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type : static
Species : Daphnia magna (Crustacea)
Exposure period :
Unit : mg/l
EC50 : = 1.25 measured/nominal
Method :
Year :
GLP : yes
Test substance :

Source : Arkema Inc. Philadelphia, PA USA
Reliability : (2) valid with restrictions
22.12.2005 (3) (24)

Type : other: modeled estimate
Species : Daphnia sp. (Crustacea)
Exposure period : 48 hour(s)
Unit : mg/l
EC50 : ca. .038 calculated

Result : ECOSAR v0.99g Class(es) Found: Epoxides

Predicted Daphnid 48-hr LC50 0.038 mg/L (ppm) *

Note: * = asterisk designates: Chemical may not be soluble enough to measure this predicted effect.
Fish and daphnid acute toxicity log Kow cutoff: 5.0
MW cutoff: 1000

Source : Arkema Inc. Philadelphia, PA USA
28.05.2004

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

Type : aquatic
Species :
Exposure period :
Unit : mg/l
EC10 : measured/nominal
EC50 : = 5000
Method :
Year :
GLP : yes
Test substance :

Source : Arkema Inc. Philadelphia, PA USA
Data provided by Dow
Reliability : (2) valid with restrictions
22.12.2005 (3) (24)

4.5.1 CHRONIC TOXICITY TO FISH

4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

4.6.1 TOXICITY TO SEDIMENT DWELLING ORGANISMS

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

4.6.3 TOXICITY TO SOIL DWELLING ORGANISMS

4.6.4 TOX. TO OTHER NON MAMM. TERR. SPECIES

4.7 BIOLOGICAL EFFECTS MONITORING

4.8 BIOTRANSFORMATION AND KINETICS

4.9 ADDITIONAL REMARKS

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

In Vitro/in vivo	:	In vitro
Type	:	Metabolism
Species	:	other: mammalian liver
Number of animals		
Males	:	
Females	:	
Doses		
Males	:	
Females	:	
Vehicle	:	
Method	:	
Year	:	1975
GLP	:	no
Test substance	:	other TS

Method : 1-Hexadecene dissolved in acetone and suspended in 0.1 M phosphate buffer, pH 7.4, was incubated with rabbit liver microsomes in the presence of an NADPH-generating system. The reaction was terminated by the addition of sodium hydroxide, and the mixture extracted with ether containing 1,2-epoxytetradecane or 1,2-dihydroxytetradecane as the internal reference for the quantitative determination of metabolites. The ethereal extract was subjected to preparative silica gel thin-layer chromatography developed in benzene-acetone (5:1). Authentic ,2-dihydroxytetradecane and 1,2-dihydroxyhexadecane or 1,2-epoxytetradecane and 1,2-epoxyhexadecane co-chromatographed as single bands at Rf 0.2 or 0.7, respectively. Each zone of the chromatogram was eluted with ethanol. The eluate from the Rf 0.2 zone was trimethylsilylated after the evaporation of the solvent and analyzed by gas-chromatography mass spectroscopy. Gas-chromatographic data (retention time: 7.4 min on a 2% OV-17 column at 210 C)and the mass spectrum were identical with those of authentic 1,2-dihydroxyhexadecane di-trimethylsilyl ether; a molecular ion peak with m/e 402 appeared together with fragment ion peaks characteristic of the glycol-TMS derivative at m/e 103 (strong intensity, TMS O CH2 +) and 299 (strong intensity, TMS--O- CH+--(CH2)13CH3). The eluate from Rf 0.7 zone was concentrated and directly analyzed by gas-chromatography-mass spectroscopy. Gas-chromatographic data (retention time: 4.5 min under the above conditions) and the mass spectrum obtained were identical with those of authentic 1,2-epoxyhexadecane; a molecular ion peak with role 240 appeared together with fragment ion peaks with m/e 57 (strong intensity) and 43.

Result : The formation of the epoxide was observed only when the olefin was incubated in the presence of the epoxide hydrolase inhibitor 1,2-epoxydecane (10 mM). These results indicate that 1-hexadecene is metabolized to 1,2-dihydroxyhexadecane via 1,2-epoxyhexadecane.

Enzymatic conversion of the epoxide to the glycol by rabbit liver microsomes has previously been reported.

Source	:	ATOFINA Chemicals Inc. Philadelphia
Test substance	:	1-Hexadecene
Conclusion	:	This study corroborates the enzymatic conversion of the

epoxide to the glycol by rabbit liver microsomes as previously reported.

Reliability : (1) valid without restriction
08.12.2005 (25)

5.1.1 ACUTE ORAL TOXICITY

Type	:	LD50
Value	:	> 5000 mg/kg bw
Species	:	rat
Strain	:	Sprague-Dawley
Sex	:	male/female
Number of animals	:	10
Vehicle	:	
Doses	:	5000 mg/kg bw
Method	:	
Year	:	
GLP	:	yes
Test substance	:	

Method : The single-dose oral toxicity was evaluated in Sprague-Dawley rats. A limit test was performed in which one group of five male and five female rats received a single oral administration of the test article at a dose of 5000 mg/kg body weight. Following dosing, the limit test rats were observed daily and weighed weekly. A gross necropsy examination was performed on all limit test animals at the time of scheduled euthanasia (day 14).

Year study performed: 1996

Result : No mortality occurred during the limit test. The most notable clinical abnormalities observed during the study included fecal/urine stain, rough haircoat, dark material around nose, scabs/reddened skin/hairloss and/or swelling on various areas, decreased defecation and soft stools. Body weight gain was noted for all animals during the test period. No significant gross internal findings were observed at necropsy on study day 14.

Source : Arkema Inc. Philadelphia, PA USA
Test condition : Yound adult rats were used.
Test substance : Vikolox (R) 16
Conclusion : Under the conditions of this test, the acute oral LD50 was estimated to be greater than 5000 mg/kg in the rat.
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
22.12.2005 (16)

5.1.2 ACUTE INHALATION TOXICITY

5.1.3 ACUTE DERMAL TOXICITY

Type	:	LD50
Value	:	> 2000 mg/kg bw
Species	:	rat
Strain	:	Sprague-Dawley
Sex	:	male/female
Number of animals	:	10

Vehicle	:	
Doses	:	2000 mg/kg
Method	:	
Year	:	
GLP	:	yes
Test substance	:	
Method	:	The single-dose dermal toxicity was evaluated on Sprague-Dawley rats. A limit test was performed in which one group of five male and five female rats received a single dermal administration of the test article. The test article was administered as received from the Sponsor. April 8, 1996 (GLP initiation date)
Result	:	No mortality occurred during the limit test. Clinical abnormalities observed during the study included urine stain and dark material around the facial area. Dermal irritation was noted at the site of test article application. Body weight loss was noted in four females during the day 0 to 7 body weight interval. One female did not regain her original body weight by study day 14. Body weight gain was noted for all other animals during the test period. No significant gross internal findings were observed at necropsy on study day 14.
Source	:	Arkema Inc. Philadelphia, PA USA
Test condition	:	On day -1, the fur was removed from the dorsal trunk area (~ 10% of the animal's body surface area) of the animals chosen for the limit test using an animal clipper. Young adult, Sprague-Dawley Crl:CD®BR VAF/Plus® rats received a dose of 2000 mg/kg body weight. The density of the test article was determined to be 0.85 g/mL. On the following day (day 0), the test article was administered dermally to approximately 10% of the body surface area (BSA). The test article was spread evenly over the test area and held in contact with the skin with an appropriately sized 4 ply porous gauze dressing backed with a plastic wrap which was placed over the gauze dressing (occlusive binding). Removal and ingestion of the test article was prevented by placing an elastic wrap over the trunk and test area. The elastic wrap was further secured with a tape harness on the cranial end of the trunk and then secured with adhesive tape around the trunk at the caudal end. After an approximate 24-hour exposure period, the gauze dressing, plastic and elastic wrap were removed and the comers of the test site delineated using a marker. Residual test article was removed using gauze moistened with distilled water followed by dry gauze. Following dosing, the limit test rats were observed daily and weighed weekly. A gross necropsy examination was performed on all limit test animals at the time of scheduled euthanasia (day 14).
Test substance	:	Vikolox 16
Conclusion	:	Under the conditions of this test, the acute dermal LD50 of Vikolox 16 was estimated to be greater than 2000 mg/kg in the rat.
Reliability	:	(1) valid without restriction

22.12.2005 (19)

Type	:	LD50
Value	:	= 10 ml/kg bw
Species	:	

Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Doses	:	
Source	:	Arkema Inc. Philadelphia, PA USA
Reliability	:	(2) valid with restrictions

22.12.2005 (13)

5.1.4 ACUTE TOXICITY, OTHER ROUTES

Type	:	LD50
Value	:	= 4.92 ml/kg bw
Species	:	rat
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Doses	:	
Route of admin.	:	i.p.
Exposure time	:	
Source	:	Arkema Inc. Philadelphia, PA USA Data provided by Dow Chemical Company
Reliability	:	(2) valid with restrictions

22.12.2005 (24)

5.2.1 SKIN IRRITATION

Species	:	rabbit
Concentration	:	undiluted
Exposure	:	Semiocclusive
Exposure time	:	4 hour(s)
Number of animals	:	6
Vehicle	:	
PDII	:	5
Result	:	highly irritating
Classification	:	irritating
Method	:	
Year	:	
GLP	:	yes
Test substance	:	
Method	:	The potential irritant and/or corrosive effects were evaluated on the skin of New Zealand White rabbits. April 8, 1996 (GLP initiation date)
Result	:	Exposure to the test article produced slight edema and blanching greater than 50% of the test site on 6/6 test sites at the 1 hour scoring interval. The dermal irritation resolved completely in all animals by study day 14. An additional dermal finding included desquamation, which was noted in all animals during the study but which resolved between days 9 and 14 in all cases.

Average scores

TIME	ERY	EDEMA
1 Hour	4	2
24 Hours	3.7	2

		48 Hours 3.3 1.2 72 Hours 3.3 1 7 Days 1.2 0 9 Days 0.8 0 10 Days 1 0 14 Days 0 0
Source	:	Arkema Inc. Philadelphia, PA USA
Test condition	:	Each of six adult, New Zealand White rabbits received a 0.5 mL dose of the test article as a single dermal application. The test article was administered as received from the Sponsor. The test article was placed in a beaker, heated and maintained in a water bath at 37°C. Test article was heated to liquefy but was not diluted to a concentration. On day -1, the fur was removed from the dorsal area of the trunk using an animal clipper. On the following day (day 0), the test article was applied to a small area of intact skin on each test animal (approximately 1 inch x 1 inch) The test article was administered under the gauze patch covered by an elastic wrap over the trunk and test area (semi-occlusive binding). The elastic wrap was then further secured with adhesive tape around the trunk at the cranial and caudal ends. After a four-hour exposure period, the elastic wrap and gauze patch were removed. Residual test article was removed using gauze moistened with distilled water followed by dry gauze. Test sites were subsequently examined and scored for dermal irritation for up to 14 days following patch removal. Animals were examined for signs of erythema and edema and the responses scored at approximately 1, 24, 48 and 72 hours and up to 14 days after patch removal according to the Macroscopic Dermal Grading System which is based on Draize.
Test substance	:	Vikolox (R) 16
Conclusion	:	Under the conditions of this test, the material is considered to be an irritant to the skin of the rabbit.
Reliability	:	(1) valid without restriction
22.12.2005		(18)
Species	:	rabbit
Concentration	:	
Exposure	:	
Exposure time	:	
Number of animals	:	
Vehicle	:	
PDII	:	3.8
Result	:	moderately irritating
Classification	:	
Method	:	
Year	:	
GLP	:	
Test substance	:	
Result	:	moderate (Draize score - 3.8)
Source	:	Arkema Inc. Philadelphia, PA USA
22.12.2005		(8)
Species	:	
Concentration	:	
Exposure	:	
Exposure time	:	

Number of animals	:	
Vehicle	:	
PDII	:	
Result	:	moderately irritating
Classification	:	irritating
Method	:	
Year	:	
GLP	:	
Test substance	:	

Source : Arkema Inc. Philadelphia, PA USA
22.12.2005 (13)

5.2.2 EYE IRRITATION

Species	:	rabbit
Concentration	:	undiluted
Dose	:	.1 ml
Exposure time	:	
Comment	:	
Number of animals	:	6
Vehicle	:	
Result	:	
Classification	:	irritating
Method	:	
Year	:	
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4

Method : The potential irritant and/or corrosive effects were evaluated on the eyes of New Zealand White rabbits. April 8, 1996 (GLP initiation date)

Result : ocular irritation score = [corneal opacity x area x 5] + [iritis x 5] + [(conjunctival redness + swelling + discharge) x 2]
The group mean irritation score was then calculated for each scoring interval based on the number of animals initially dosed in each group.

Exposure to the test article produced iritis in 2/6 test eyes at the 1 hour scoring interval which resolved completely in the affected eyes by the 24 hour scoring interval. Conjunctivitis (redness, swelling and discharge) was noted in 6/6 test eyes at the 1 hour scoring interval. The conjunctival irritation resolved completely in all animals by study day 7. No corneal opacity, iritis or conjunctivitis was observed in the control eyes.

Slightly irritating, Draize index 2 (110 = Maximum possible score)

Source : Arkema Inc. Philadelphia, PA USA

Test condition : Each of six rabbits received a 0.1 mL dose of the test article in the conjunctival sac of the right eye. The test article was heated in a 37°C water bath and maintained at room temperature. The test article was heated to liquefy but was not diluted. The contralateral eye of each animal remained untreated and served as a control.

Prior to dosing, eyes of each animal were examined for ocular irritation with the aid of an auxiliary light source and the corneal surface was examined using fluorescein sodium dye. Animals exhibiting ocular irritation,

preexisting comeal injury or fluorescein dye retention were not used on study.

Group	Concentration Instilled	Amount	No. of Animals Males	Females
No Rinse	100%	0.1 mL	1	5

The eyes were macroscopically examined with the aid of an auxiliary light source for signs of irritation at 1, 24, 48 and 72 hours and up to 7 days after dosing according to the Ocular Grading System based on Draize. Following macroscopic observations at the 24 hour scoring interval, the fluorescein examination procedure was repeated on all test and control eyes and any residual test article was gently rinsed from the eye at this time (if possible) using physiological saline. If any fluorescein findings were noted at 24 hours, a fluorescein exam was conducted on the affected eyes at each subsequent interval until a negative response was obtained.

Test substance : Vikolox (R) 16
Conclusion : Under the conditions of this test, this substance is considered to be an irritant to the ocular tissue of the rabbit.
Reliability : (1) valid without restriction
22.12.2005 (20)

Species : rabbit
Concentration :
Dose :
Exposure time :
Comment :
Number of animals :
Vehicle :
Result : slightly irritating
Classification :
Method : Draize Test
Year :
GLP :
Test substance :

Result : minor transient conjunctival irritation (Draize score - 2.0 at 24 hours)
Source : Arkema Inc. Philadelphia, PA USA
22.12.2005 (8)

Species :
Concentration :
Dose :
Exposure time :
Comment :
Number of animals :
Vehicle :
Result : not irritating
Classification : not irritating
Method :
Year :
GLP :
Test substance :

Source : Arkema Inc. Philadelphia, PA USA
22.12.2005 (13)

5.3 SENSITIZATION

Type	:	Buehler Test
Species	:	guinea pig
Concentration	:	1st: Induction 50 % occlusive epicutaneous 2nd: Induction 50 % occlusive epicutaneous 3rd: Induction 50 % occlusive epicutaneous
Number of animals	:	20
Vehicle	:	other: mineral oil
Result	:	sensitizing
Classification	:	
Method	:	
Year	:	
GLP	:	yes
Test substance	:	other TS

Method : This study was performed to assess the dermal sensitization potential (delayed contact hypersensitivity) in Hartley-derived albino guinea pigs when administered by multiple topical applications. May 14, 1996 (GLP initiation date).

Result : A. Topical Range-Finding Studies: A test article concentration of 50% w/v in mineral oil was the maximum concentration that produced irritation. A concentration of 5% w/v in mineral oil was the highest non-irritating concentration and was therefore considered appropriate for challenge.
B. Sensitization Study: Following Induction I @ 50% w/v in mineral oil, dermal scores of 1 were noted in 8/20 test animals at the 24 hour scoring interval and dermal scores of 1 to 2 (three with very slight edema) were noted in 13/20 test animals at the 48 hour scoring interval. At Induction II, which was performed on the same test site and concentration as Induction I, dermal scores of 2 to 3 (all with very slight to moderate edema and some with blanching and/or eschar) were noted in all test animals at both the 24 and 48 hour scoring intervals. This increase in dermal scores from Induction I to II may be partially attributed to primary irritation since the animals were dosed on the same test site. Following Induction Ill at 50% w/v, dermal scores of 2 to 3 (all with very slight to slight edema, 12/20 with blanching and 1/20 with eschar) were again noted in all test animals at the 24 hour scoring interval. At the 48 hour scoring interval, dermal scores of 1 to 3 (17/20 with very slight to slight edema and 7/20 with blanching) were noted in all test animals. Since Induction III was dosed on a naive test site, the increase in dermal scores when compared with Induction 1 is probably an indication of sensitization.
Following challenge with 5% w/v in mineral oil, dermal scores of 1 to 2 (two with very slight edema) were noted in 11/20 test animals at the 24 hour scoring interval. At the 48 hour scoring interval, dermal scores of 1 were noted in 3/20 test animals. Dermal reactions in the remaining test and all challenge control animals were limited to scores of 0 to t. Group mean dermal scores were noted to be slightly higher in the test animals as compared with the challenge control animals.
Following rechallenge with 5% w/v in mineral oil, dermal scores of 1 to 2 (two with very slight edema) were noted in 10/20 test animals at the 24 hour scoring interval. At the 48 hour scoring interval, dermal scores of 1 to 2 (one with very slight edema) were noted in 6/20 test animals. Dermal reactions in the remaining test and all challenge control

animals were limited to scores of 0 to +. Group mean dermal scores were noted to be slightly higher in the test animals as compared with the challenge control animals.
Following rechallenge with 15% w/v in mineral oil, dermal scores of 1 to 2 (most with very slight edema) were noted in 20/20 test animals at the 24 hour scoring interval and in 19/20 test animals at the 48 hour scoring interval. Dermal reactions in the remaining test and all challenge control animals were limited to scores of 0 to +/-. Group mean dermal scores were noted to be higher in the test animals as compared with the challenge control animals.
Following rechallenge with 100% mineral oil, dermal scores of 0 to +/- were noted in all test and challenge control animals. Group mean dermal scores were noted to be similar in the test animals as compared with the challenge control animals.

Source : Arkema Inc. Philadelphia, PA USA

Test condition : The test article was heated in a 37°C water bath (until liquefied).
Young adult, Hartley-derived albino guinea pigs were used.
Prior to dose administration, guinea pigs were weighed and the hair removed from the right and left side of the animals with a small animal clipper.
Induction was accomplished with a 50% solution applied to 10 male and 10 female guinea pigs on days 1, 7 and 13.
On the day prior to challenge dose administration, the test and challenge control animals were weighed and the hair was removed from the right side of the animals. On the day following clipping (day 27), a 5% solution was administered for 6 hours.
A rechallenge was conducted in order to substantiate and clarify the challenge results. On the day prior to rechallenge dose administration, all test and challenge control animals were weighed and the hair was then removed from the right side and left side of the animals. On the day following clipping (day 34), challenge doses of 5% and 15% were applied on separate sites for 6 hours.

Test substance : Vikolox (R) 16

Conclusion : Based on the results of this study, this material is considered to be a contact sensitizer in guinea pigs. The results of the hexylcinnamaldehyde historical control study demonstrated that the test design utilized would detect potential contact sensitizers.

Reliability : (1) valid without restriction
22.12.2005 (17)

5.4 REPEATED DOSE TOXICITY

Type :
Species : rat
Sex : male/female
Strain : Fischer 344
Route of admin. : dermal
Exposure period : 13 weeks
Frequency of treatm. : daily; 5/week
Post exposure period :
Doses : 0, 62.5 mg/kg, 125, 250, 500, 1000; conc : 0, 3.75, 7.5, 15. 30, 60%
Control group : yes, concurrent vehicle
LOAEL : = 125 mg/kg bw

Method : Method/guideline followed 90 day study

Test type Dermal skin painting
GLP (Y/N) study was audited by NTP

Year (study performed) 1979
Species rat
Strain F344
Route of administration dermal
Doses/concentration levels 0, 62.5,125, 250, 500, 1000
conc : 0, 3.75, 7.5, 15. 30, 60%

Sex M & F
Exposure period 90 days
Frequency of treatment 5 days/week
Control group and treatment Vehicle control
Post exposure observation period 5 days
Statistical methods none
Age at study initiation 7 weeks
No. of animals per sex per dose 10; group housed 5/sex/cage
Vehicle Acetone
Dose volume adjusted on weight basis
Dose concnetration 4% - 60%
Clinical Observations Body weights weekly; 2x daily checks for signs and mortality, detailed observations 1/wk
Necropsy Gross pathology; organs examined: skin, lymph nodes (mandibular, mesenteric) mammary gland, salivary gland, thigh muscles, sciatic nerve, bone marrow, thymus, larynx, trachea, lungs and bronchi, heart, thyroid, parathyroid, esophagus, stomach, duodenum, jejunum, ileum, colon, rectum, liver, pancreas, spleen, kidneys, adrenals, bladder, seminal vescicles, prostate, testes, ovaries, uterus, nasal cavity, brain, pituitary, eyes, external and middle ear, spinal cord.

Remark : The data presented here were extracted from the records maintained at the NTP archives.
Pathology QUALITY ASSESSMENT
REPORT OF THE SUBCHRONIC STUDY OF EPOXY HEXADECANE (C55538)
IN Fischer 344 Rats and B6C3F1 Mice

RATS
There were lesions observed in this study. These skin lesions (site of application) were manifested in a variety of changes. changes consisted of hyperkeratosis, parakeratosis, acanthosis, necrosis of cells, and necrosis with varying degrees of inflammation. In more severe cases, mostly high dose and mid dose animals, there was ulceration of the skin accompanied with acute and chronic inflammation. In one case, high dose male, there were pyogenic granulomas deep in the dermis and muscle.
Lung lesions seen in this study are suggestive of being Sendi virus induced.
The reviewing pathologist concluded that there were no discrepancies noted which should alter the doses recommended for the chronic study.

Result : Body weights: consistently slightly to moderately reduced @ 500 & 1000 for males; at termination ~20 and 35% lower than controls, and from the second week of dosing @ 250, 500, and 1000 slightly to moderately reduced for females; at termination 9, 27, 4, and 70% lower than controls

Clinical signs: 62.5 mg/kg: (2 of 10 males) dark brown spots on treated areas weeks 3 - 8; weeks 9 - 13 hyperemic treatment area

250 mg/kg: weeks 3 - 9: all males exfoliation of stratum corneum; weeks 10 - 13 - sores on backs

500 mg/kg: weeks 3 - 8 - all animals exfoliation of stratum corneum and alopecia; in addition during weeks 9 -13 erythema and rough coats in some animals; some females thin

1000 mg/kg: weeks 1 - 3 rough coats and slight erythema; weeks 4 - 13 in addition exfoliation of the stratum corneum, week 5 - 13 dark urine, emaciation primarily in females, alopecia, sores in treated area.

Microscopic findings are limited to the skin and site of application. Deep dermal abscesses, focal ulceration, inflammation were reported.

Murine virus Antibody Determinations: PVM titers ranged from 80 - 40 in10/10 animals, KRV titers of 160 to 640 in 4/0 animals and Sendi titers of 80 - 320 in 10/10 animals.

Mortality: none prior to study termination

Source : Arkema Inc. Philadelphia, PA USA

Test substance : 1,2-epoxyhexadecane, Viking chemical Lot # P-2-305; Clear viscous liquid no precipitate; checked for stability and purity every 4 months; Titration with tetrabutyl ammonium iodide and standard perchloric acid indicates a purity of 91.8%; stable in acetone for 7 days diluted up to 10%.

Chemical Specification from Viking Chemicals Technical Bulletin for material used in NTP bioassay and supporting studies:
Acid Value (mg KOH/g) 0.20 max
Oxirane Oxygen (theory - 6.66%) 6.12% min
Peroxide number meq O/ 1,000 g 10 max
Described as colorless cloudy liquid

Conclusion : LOAEL = 125 mg/kg. The most suitable level for a chronic study would be 125 mg/kg.

Reliability : (2) valid with restrictions
During 1983 the US National Toxicology Program (NTP) staff evaluated a variety of problems associated with studies performed at the contractor, Gulf South Research Institute. A comprehensive quality assurance audit was performed and the decision was made to maintain the existing records at the NTP archives and to release limited data, without interpretations or conclusions as a special abridged report on the GSRI studies.

The data from the 1,2-epoxyhexadecane study was placed in a category considered data not fully reliable. The explanation is: None of the flaws in any study in this category would, if taken individually, seriously impact on the study; however, when viewed in toto, and in relation to the other studies or corporately, the collective flaws lead one to question the interpretability or unequivocal validity of the results. In most cases the flaws involve omission rather than commission and therefore a greater degree of good faith is required in accepting the results than the usual or typical study conducted for the NTP.

In summary, while we have some confidence that the qualitative results (target organ identification and pathology) would be reasonably similar if the study was conducted again using the same exposure regimens, there is less certainty than one would desire in this respect and the quantitative results (magnitude of response) should be considered still less certain.

Flag : Critical study for SIDS endpoint
22.12.2005 (12)

Type :
Species : rat
Sex : male/female
Strain : Fischer 344
Route of admin. : dermal
Exposure period : 14 days
Frequency of treatm. : daily
Post exposure period :
Doses : O, 2.5%, 5%, 10%, 20%, 40% applied 0.6 ml
Control group : yes, concurrent vehicle
LOAEL : = 2.5 %
Method :
Year :
GLP : no data
Test substance : other TS

Method : Control group and treatment Vehicle acetone
Post exposure observation period 5 days
Statistical methods None
Age at study initiation 8 weeks
No. of animals per sex per dose 5
Vehicle Acetone
Clinical Observations Body weights weekly
Necropsy Gross pathology

Remark : The data presented here were extracted from the records maintained at the NTP archives.

Result : Clinical signs: Rough coats, tissue necrosis of treated areas, dark urine; dose related body weight depression at all levels
Gross necropsy findings: desquamation, alopecia, focal irritation of the skin
Mortality: 1 female @ 20% and 2 females at 40%

Source : Arkema Inc. Philadelphia, PA USA

Test substance : 1,2-epoxyhexadecane, Viking chemical Lot # P-2-305; Clear viscous liquid no precipitate; checked for stability and purity every 4 months; Titration with tetrabutyl ammonium iodide and standard perchloric acid indicates a purity of 91.8%; stable in acetone for 7 days diluted up to 10%.

Conclusion : Body weight data indicate a dose related effect with all test groups gaining less weight than controls and the 40% group losing more than 10 grams of body weight. At the 5% level and above, both sexes gained 19 to 150% less than controls. At the 2.5% level the males gained -14% and the females -6% relative to controls. Pathological changes consisted mostly of deaquamation and depilation at 10% and above.

Reliability : (4) not assignable
22.12.2005 (11)

Type :
Species : mouse
Sex : male/female

Strain	:	B6C3F1
Route of admin.	:	dermal
Exposure period	:	13 weeks
Frequency of treatm.	:	5 days/week
Post exposure period	:	
Doses	:	0, 62.5 , 125, 250, 500, 1000 mg/kg
Control group	:	yes, concurrent vehicle
LOAEL	:	= 125 mg/kg bw
Method	:	
Year	:	
GLP	:	
Test substance	:	other TS

Method :

Test type Dermal skin painting
GLP (Y/N) no
Year (study performed) 1979
Species Mouse
Strain B6C3F1
Route of administration Dermal; applied to shaved skin of back ~ 1 sq inch area
Duration of test 13 weeks
Doses/concentration levels 0, 62.5 mg/kg, 125, 250, 500, 1000; conc : 0, 0.94%, 1.875, 3.75, 7.5, 15%
Sex M & F
Exposure period 90 days
Frequency of treatment 5 days/week
Control group and treatment Vehicle control
Post exposure observation period 5 days
Statistical methods None
Age at study initiation 7 weeks
No. of animals per sex per dose 10; group housed 5/sex/cage
Vehicle Acetone
Clinical Observations Body weights weekly; 2x daily checks for signs and mortality, detailed observations 1/wk;
Necropsy
Gross pathology; organs examined: skin, lymph nodes (mandibular, mesenteric) mammary gland, salivary gland, thigh muscles, sciatic nerve, bone marrow, thymus, larynx, trachea, lungs and bronchi, heart, thyroid, parathyroid, esophagus, stomach, duodenum, jejunum, ileum, colon, rectum, liver, pancreas, spleen, gall bladder, kidneys, adrenals, bladder, seminal vescicles, prostate, testes, ovaries, uterus, nasal cavity, brain, pituitary, eyes, external and middle ear, spinal cord.

Remark :

Pathology QUALITY ASSESSMENT
REPORT OF THE SUBCHRONIC STUDY OF EPOXY HEXADECANE (C55538)
IN Fischer 344 Rats and B6C3F1 Mice

MICE
Dose related lesions were encountered in the skin (target organ). The reviewing pathologist concluded that there were no discrepancies noted which should alter the recommendations for the chronic study. The lung lesions seen in this study are suggestive of being Sendi virus induced.

Result :

Body weights: reduced body weights in males at > 250; beginning in the fourth week the mean body weights of the 1000 and 250 were slightly to moderately and 500 very slightly to slightly less than the controls. Mean body weights @ 500 dipped markedly during week 6 but recovered to near control values in week 7; mean body weights recovered

to near controls for all doses by end of the study; mean body weights of females varied too widely for any meaningful relationship to treatment.

Clinical signs: cutaneous reactions: exfoliation of the corneum layer of the skin, alopecia, hyperemia, and or blanching at application site @ > 250 in males and @ 1000 in females

Clincial observations: males:Control - sores on back likely due to fighting
250 mg/kg: sores on back likely due to fighting; Weeks 3 - 6 treatment area looks pale; week 7 some with thin appearance, Week 8 -- 2 found dead
500 mg/kg: weeks 3 - 6 - all animals exfoliation of stratum corneum and blanching of the skin; week 7 -- 4 found dead, survivors appear thin; weeks 7 -13: conditions of survivors improves
1000 mg/kg: weeks 1 - 2 exfoliation of the stratum corneum and alopecia of treated area; week 3 -- one found dead; week 7 -- 6 found dead; week 11 3 animals with sores on dorsal area; week 12 -- one found dead.

Clinical observations, females:250 mg/kg: weeks 3 - dark patches or blanching on treated area (1 each) Week 7 -- 3 found dead; Weeks 8-9 rough coats, thin; Weeks 8 - 13: conditions improve
500 mg/kg: Week 7: 3 found dead, others thin; Week 8: 1 found dead; Weeks 9 - 13 condition improves1000 mg/kg: Week 1 slight erythema of treated area; week 2: exfoliation of the stratum corneum of treated area; weeks 3 - 6: exfoliation of the stratum corneum and alopecia of treated area; Week 6 one found dead; Week 7 -- 3 found dead; Weeks 7 - 13: thin appearance and continued dermal effects.

Microscopic findings -- hyperkeratosis (minimal to moderate) in 14 mice, parakeratosis in 3 mice, and epithelial hyperplasia in 8 mice. Except for the tissue changes in the skin of treated mice there were no tissue changes attributable to the effects of the test material in any of the treated mice examined. Mortality: 2m/3f @ 250; 4m/4f @ 500; 8m/4f @ 1000 mg/kg; most deaths occurred during weeks 6 - 8

Source : Arkema Inc. Philadelphia, PA USA

Test substance : 1,2-epoxyhexadecane, Viking chemical Lot # P-2-305; Clear viscous liquid no precipitate; checked for stability and purity every 4 months; Titration with tetrabutyl ammonium iodide and standard perchloric acid indicates a purity of 91.8%; stable in acetone for 7 days diluted up to 10%.

Conclusion : LOAEL - 125 mg/kg. Treatment related dermal lesions

Reliability : (2) valid with restrictions
During 1983 the US National Toxicology Program (NTP) staff evaluated a variety of problems associated with studies performed at the contractor, Gulf South Research Institute. A comprehensive quality assurance audit was performed and the decision was made to maintain the existing records at the NTP archives and to release limited data, without interpretations or conclusions as a special abridged report on the GSRI studies.

The data from the 1,2-epoxyhexadecane study was placed in a

category considered data not fully reliable. The explanation is: None of the flaws in any study in this category would, if taken individually, seriously impact on the study; however, when viewed in toto, and in relation to the other studies or corporately, the collective flaws lead one to question the interpretability or unequivocal validity of the results. In most cases the flaws involve omission rather than commission and therefore a greater degree of good faith is required in accepting the results than the usual or typical study conducted for the NTP.

In summary, while we have some confidence that the qualitative results (target organ identification and pathology) would be reasonably similar if the study was conducted again using the same exposure regimens, there is less certainty than one would desire in this respect and the quantitative results (magnitude of response) should be considered still less certain.

22.12.2005 (11)

Type :
Species : mouse
Sex : male/female
Strain : B6C3F1
Route of admin. : dermal
Exposure period : 14 days
Frequency of treatm. : daily
Post exposure period : 5 days
Doses : O, 2.5%, 5%, 10%, 20%, 40% applied 0.2 ml
Control group : yes, concurrent vehicle
NOAEL : = 5 %
LOAEL : = 10 %
Method :
Year :
GLP :
Test substance : other TS

Method : Method/guideline Range finding study for 90 day study

Test type	14 day dermal
Year (study performed)	1979
Species	mouse
Strain	B6C3F1
Route of administration	dermal
Frequency of treatment	daily
Vehicle	acetone
Post exposure observation period	5 days
Statistical methods	none
Age at study initiation	8 weeks
No. of animals per sex per dose	5
Clinical Observations	Body weights weekly
Necropsy	Gross pathology

Remark : The data presented here were extracted from the records maintained at the NTP archives.

Result : Body weights (grams)

	Males		Females	
	Start	End	Start	End
Control	28.0	28.4	20.4	22.0
2.5%	28.0	28.6	20.4	21.8
5%	27.6	30.2	19.4	22.6
10%	28.4	27.2	20.0	22.0
20%	28.8	26.4	19.4	18.6
40%	27.6	23.0	20.8	18.2

Gross necropsy records showed alopecia and small skin ulcers with the alopecia varying from focal area at the application site to 90% of the body. This alopecia was assumed to be compound related since large patches of hair were observed falling out during the test and this was not seen in controls. Clinical signs included tissue necrosis loss of equilibrium and difficulty walking. Mortality: all high dose females and I high dose male died during the 5 day post dosing observation period. No other mortalities.

Source : Arkema Inc. Philadelphia, PA USA

Test substance : 1,2-epoxyhexadecane, Viking chemical Lot # P-2-305; Clear viscous liquid no precipitate; checked for stability and purity every 4 months; Titration with tetrabutyl ammonium iodide and standard perchloric acid indicates a purity of 91.8%; stable in acetone for 7 days diluted up to 10%.

Conclusion : Body weight data indicate a probable toxic effect at 10% and above in males and 20% and above in females.

Reliability : (4) not assignable

22.12.2005 (11)

5.5 GENETIC TOXICITY 'IN VITRO'

Type :
System of testing :
Test concentration :
Cycotoxic concentr. :
Metabolic activation :
Result : negative
Method :
Year :
GLP :
Test substance :

Source : Arkema Inc. Philadelphia, PA USA

Reliability : (2) valid with restrictions

Flag : Critical study for SIDS endpoint

22.12.2005 (1)

Type : Salmonella typhimurium reverse mutation assay
System of testing :
Test concentration :
Cycotoxic concentr. :
Metabolic activation :
Result : negative
Method :
Year :
GLP :
Test substance :

Source : Arkema Inc. Philadelphia, PA USA

Flag : Critical study for SIDS endpoint

22.12.2005 (22)

Type : Sister chromatid exchange assay
System of testing : CHO cells
Test concentration :
Cycotoxic concentr. :
Metabolic activation :
Result : negative

Method	:	
Year	:	
GLP	:	
Test substance	:	
Source	:	Arkema Inc. Philadelphia, PA USA
Reliability	:	(2) valid with restrictions
Flag	:	Critical study for SIDS endpoint
22.12.2005		(15)
Type	:	Sister chromatid exchange assay
System of testing	:	Chinese Hamster Cells
Test concentration	:	
Cycotoxic concentr.	:	
Metabolic activation	:	
Result	:	negative
Method	:	
Year	:	
GLP	:	
Test substance	:	
Source	:	Arkema Inc. Philadelphia, PA USA
22.12.2005		(23)
Type	:	Ames test
System of testing	:	TA98, TA100, TA1535, TA1537, TA1538
Test concentration	:	
Cycotoxic concentr.	:	
Metabolic activation	:	
Result	:	negative
Method	:	
Year	:	
GLP	:	
Test substance	:	
Source	:	Arkema Inc. Philadelphia, PA USA
22.12.2005		(5)
Type	:	Mouse lymphoma assay
System of testing	:	
Test concentration	:	
Cycotoxic concentr.	:	
Metabolic activation	:	
Result	:	positive
Method	:	
Year	:	
GLP	:	
Test substance	:	
Source	:	Arkema Inc. Philadelphia, PA USA
22.12.2005		(6)
Type	:	Salmonella typhimurium reverse mutation assay
System of testing	:	
Test concentration	:	
Cycotoxic concentr.	:	
Metabolic activation	:	
Result	:	negative
Method	:	
Year	:	
GLP	:	
Test substance	:	

Source : Arkema Inc. Philadelphia, PA USA
22.12.2005 (9)

5.6 GENETIC TOXICITY 'IN VIVO'

5.7 CARCINOGENICITY

Species : rat
Sex : male/female
Strain : Fischer 344
Route of admin. : dermal
Exposure period : 2 years
Frequency of treatm. : 5 days/week for 103 weeks
Post exposure period : 1 week
Doses : 125, 62.5 mg/kg
Result :
Control group : yes, concurrent vehicle
Method :
Year :
GLP :
Test substance :

Method : Method/guideline followed chronic bioassay
Test type Dermal skin painting
GLP (Y/N) study was audited by NTP
Year (study performed) 1980
Species rat
Strain F344
Route of administration dermal
Doses/concentration levels 0, 62.5,125
conc : 0, 3.75, 7.5 (adjusted based on body weight to allow for administration of 600 microliters)
Sex M & F
Exposure period 103 weeks
Frequency of treatment 5 days/week
Control group and treatment Vehicle control
Post exposure observation period 5 days
Statistical methods Fischers exact test
no. of animals per sex per dose 50; group housed 5/sex/cage
Vehicle Acetone
Clinical Observations Body weights weekly for first thirteen weks then monthly; 2x daily checks for signs and mortality, detailed observations 1/wk and palpated for masses
Interim sacrifices None
Special studies None

Moribund animals need for unscheduled sacrifice and necropsy determined by veterinarian or toxicologist; tissues preserved

Necropsy

Gross pathology: gross lesions and tissue masses and regional lymph nodes

organs examined:
adrenals,
bladder,
blood smear
brain (3 sections),
colon,
duodenum,
ear, external and middle
esophagus,
eyes,
heart,
ilem,
jejunum,
kidneys,
larynx,
liver,
lungs and bronchi,
lymph nodes (mandibular, mesenteric)
mammary gland,
nasal cavity,
ovaries,
pancreas,
parathyroid,
pituitary,
prostate,
rectum,
salivary gland,
sciatic nerve,
seminal vesicles,
skin,
small intestine (one section)
spinal cord.
spleen,
sternebrae, femur or vertebrae including bone marrow,
stomach,
testes,
thigh muscle,
thymus,
thyroid,
trachea,
uterus,

Remark : The data presented here were extracted from the records maintained at the NTP archives.

Result : No compound related toxicological effects were observed during most of the chronic study. No striking toxicological effects were observed when observation data for each treatment group was compared to controls.

Some non significant differences were seen between the groups for non-tumour pathology. Changes noted in the skin were significant and are listed below by sex and dose group

	Males %			Females %		
	C	low	high	c	low	high
Inflammation						
focal	2				2	
chronic		2	6		8	4
chronic & focal		2			4	4
acute					2	

acute & focal				2					
acute & chronic						2			
Hyperplasia									
NOS	2	4	32		26	26			
epithelial	2								
focal	2			2					
Hyperkeratosis		12	18		2	12			
Sclerosis									
dermis	2								

It is apparent that the test material is a skin irritant and induces proliferative changes when applied topically.

No consistent compound related reduction in body weight occurred in any of the treatment groups. Periodic weight fluctuations were attributed to problems with the automatic watering system.
Results of Post Pathology Working Group (PWG)
PATHOLOGY NARRATIVE OF 1,2-EPOXYHEXADECANE (C55538) IN B6C3Fl MICE AND FISCHER 344 RATS August 11, 1983

Neoplastic Lesions
There was reported an increased incidence of adenomas of the anterior pituitary gland in female rats. These neoplasms are well circumscribed usually solid masses of a single cell type that are moderately well demarcated from, and compress, surrounding tissue. Areas of trabecular formation are sometimes found and cavernous, blood-filled vessels often give the impression of hemorrhage in early lesions. In older, larger tumors the pools of blood may be lined with tumor cells rather than endothelium.
The PWG found additional tumors in all groups of female rats. in addition, there was unequal sampling among the groups with the greatest number of tissue specimens available in the test groups.

Pituitary -Adenomas - Female Rats

	Control	Low Dose	High Dose
Original	13/50 (26%)	21/47 (45%)	18/48 (38%)
PWG	19/79 (24%)	25/104 (24%)	24/90 (26%)

Source : Arkema Inc. Philadelphia, PA USA
Conclusion : RATS Pathology Working Group CONCLUSIONS
1,2-Epoxyhexadecane in a two-year skin paint study did not produce any compound related neoplastic or systemic toxic lesions in F344 rats.
Reliability : (2) valid with restrictions
During 1983 the US National Toxicology Program (NTP) staff evaluated a variety of problems associated with studies performed at the contractor, Gulf South Research Institute. A comprehensive quality assurance audit was performed and the decision was made to maintain the existing records at the NTP archives and to release limited data, without interpretations or conclusions as a special abridged report on the GSRI studies.

The data from the 1,2-epoxyhexadecane study was placed in a category considered data not fully reliable. The explanation is: None of the flaws in any study in this

category would, if taken individually, seriously impact on the study; however, when viewed in toto, and in relation to the other studies or corporately, the collective flaws lead one to question the interpretability or unequivocal validity of the results. In most cases the flaws involve omission rather than commission and therefore a greater degree of good faith is required in accepting the results than the usual or typical study conducted for the NTP.

In summary, while we have some confidence that the qualitative results (target organ identification and pathology) would be reasonably similar if the study was conducted again using the same exposure regimens, there is less certainty than one would desire in this respect and the quantitative results (magnitude of response) should be considered still less certain.

22.12.2005 (11)

Species	:	mouse
Sex	:	male/female
Strain	:	B6C3F1
Route of admin.	:	dermal
Exposure period	:	2 years
Frequency of treatm.	:	5 days/week for 103 weeks
Post exposure period	:	1 week
Doses	:	125, 62.5 mg/kg
Result	:	
Control group	:	yes, concurrent vehicle
Method	:	
Year	:	1980
GLP	:	
Test substance	:	

Method :

Test type Dermal skin painting
GLP (Y/N) Study audited by NTP
Year (study performed) 1980
Species Mouse
Strain B6C3F1
Route of administration Dermal; applied to shaved skin of back ~ 1 sq inch area
Duration of test 103 weeks
Dose levels 0, 62.5, 125 mg/kg concnetrations adjusted based on body weight to allow administration of 200 microliters.
Sex M & F
Exposure period 103 weeks
Frequency of treatment 5 days/week
Control group and treatment Vehicle control
Post exposure observation period 5 days
Statistical methods None
No. of animals per sex per dose 50; group housed 5/sex/cage
Vehicle Acetone
Clinical Observations Body weights weekly for first 13 weeks then monthly; 2x daily checks for signs and mortality, detailed observations 1/wk and palpated for massed
Interim sacrifices None
Special studied None

Moribund animals need for unscheduled sacrifice and necropsy determined by veterinarian or toxicologist; tissues preserved

Necropsy
Gross pathology; organs examined: skin, lymph nodes (mandibular, mesenteric) mammary gland, salivary gland, thigh muscles, sciatic nerve, bone marrow, thymus, larynx, trachea, lungs and bronchi, heart, thyroid, parathyroid, esophagus, stomach, duodenum, jejunum, ileum, colon, rectum, liver, pancreas, spleen, gall bladder, kidneys, adrenals, bladder, seminal vescicles, prostate, testes, ovaries, uterus, nasal cavity, brain, pituitary, eyes, external and middle ear, spinal cord.

Remark : The data presented here were extracted from the records maintained at the NTP archives.

Result : Pathology Working Group
PATHOLOGY NARRATIVE OF 1,2-EPOXYHEXADECANE (C55538) IN B6C3Fl MICE AND FISCHER 344 RATS August 11, 1983

1. All groups of male mice, including controls, had a high incidence of subcutaneous, mesenchymal neoplasms as follows:

Subcutaneous Neoplasms - Male Mice

	Control	Low Dose	High Dose
Malignant			
Sarcoma NOS	1	3	4
Fibrosarcoma	2	4	5
Neurofibrosarcoma	1	-	-
Combined	4 (8%)	7 (14%)	9 (18%)
Benign			
Fibroma	1	1	4
Total Combined Incidence	5 (10X)	8 (16%)	13 (26%)

The distribution of the lesions on the body were back 19, abdomen 3, side 2 and leg and axilla one each. Only one fibrosarcoma was clearly identified as occurring at the application site. The tumors were all visible grossly and varied in size up to 6.0 x 3.5 x 2.4 cm.

Microscopically fibromas are composed of fusiform or stellate cells with pale, ovoid or rounded nuclei. The cells produce interlacing bundles of collagen fibers which may be densely packed or loosely arranged as if separated by edema or a mucinous ground substance. The tumors are relatively well circumscribed and non-invasive. Fibrosarcomas are more cellular and produce less collagen. They are locally invasive and may metastasize. Neurofibrosarcomas are similar to fibrosarcomas. They are characterized by bundles of cells and fibers that are arranged in whorls which when cut longitudinally produce a herring :one pattern. They are believed to arise from nerve sheaths. Many pathologists do not differentiate them from fibrosarcomas. Sarcoma NOS are extremely cellular tumors which may contain large bizarre nuclei, mitotic figures and multinucleated giant cells. A pattern of interwoven bundles of fusiform cells may be apparent but collagen fibers are difficult to demonstrate in any quantity even with polarized light. They may be locally invasive and metastasize.

2. There was a modest increase in the incidence of hepatocellular adenomas in all groups of male mice as follows:

Hepatocellular Neoplasms - Male Mice

	Control	Low Dose	High Dose
Adenoma	13 (27%)	14 (29%}	11 (22%)
Carcinoma	4 (8%)	10 (21%) 9 (18%)	
Combined Incidence	17 (34%)	24 (48%)	20 (40%)

The incidence of hepatocellular carcinoma was low in control male mice and average for treated animals.

Hepatocellular adenomas microscopically have well defined borders that may be scalloped and which compress the surrounding parenchyma. There are variations in cell morphology and absence of triads. Organization is of a solid or trabecular type or a combination of both. Solid areas are composed of closely packed cells resembling normal hepatocytes in which sinusoids are rarely seen. The trabecular type has a clear cut cord structure with sinusoids separating the cords. Cords may radiate from blood vessels giving a pseudo-lobular appearance. In some tumors fatty change or vacuolation of the cytoplasm is prominent.

Hepatocellular carcinomas also occur in solid, trabecular and mixed patterns. Cells comprising the solid pattern vary greatly in cell and nuclear size and giant cells with large hyperchromatic nuclei are frequently present. The trabecular pattern differs from that of the adenoma in that the cords are many cells thick. Dilation of the sinusoids produces disruption of the regular trabecular pattern and necrosis and hemorrhage is common.

Source : Arkema Inc. Philadelphia, PA USA

Test substance : 1,2-epoxyhexadecane, Viking chemical Lot # P-2-305; Clear viscous liquid no precipitate; checked for stability and purity every 4 months; Titration with tetrabutyl ammonium iodide and standard perchloric acid indicates a purity of 91.8%; stable in acetone for 7 days diluted up to 10%.

Conclusion : The pathology working group concluded that 1,2-epoxyhexadecane in a two year skin painting study was associated with a dose-related increase in subcutaneous mesenchymal neoplasms in male B6C3F1 mice. A clear relationship between the location of the neoplasms and the area of skin exposure to the test compound cannnot be established from the data except for one tumor.

There were no other neoplastic or systemic toxic compound related effects in B6C3F1 mice. The pathology working group considered the modest increase in hepatocellular tumors in male mice not to be of biological significance.

Reliability : (2) valid with restrictions
During 1983 the US National Toxicology Program (NTP) staff evaluated a variety of problems associated with studies performed at the contractor, Gulf South Research Institute. A comprehensive quality assurance audit was performed and the decision was made to maintain the existing records at the NTP archives and to release limited data, without interpretations or conclusions as a special abridged report on the GSRI studies.

The data from the 1,2-epoxyhexadecane study was placed in a category considered data not fully reliable. The

explanation is: None of the flaws in any study in this category would, if taken individually, seriously impact on the study; however, when viewed in toto, and in relation to the other studies or corporately, the collective flaws lead one to question the interpretability or unequivocal validity of the results. In most cases the flaws involve omission rather than commission and therefore a greater degree of good faith is required in accepting the results than the usual or typical study conducted for the NTP.

In summary, while we have some confidence that the qualitative results (target organ identification and pathology) would be reasonably similar if the study was conducted again using the same exposure regimens, there is less certainty than one would desire in this respect and the quantitative results (magnitude of response) should be considered still less certain.

22.12.2005 (11)

5.8.1 TOXICITY TO FERTILITY

5.8.2 DEVELOPMENTAL TOXICITY/TERATOGENICITY

5.8.3 TOXICITY TO REPRODUCTION, OTHER STUDIES

5.9 SPECIFIC INVESTIGATIONS

5.10 EXPOSURE EXPERIENCE

5.11 ADDITIONAL REMARKS

6.1 ANALYTICAL METHODS

6.2 DETECTION AND IDENTIFICATION

7.1 FUNCTION

7.2 EFFECTS ON ORGANISMS TO BE CONTROLLED

7.3 ORGANISMS TO BE PROTECTED

7.4 USER

7.5 RESISTANCE

8.1 METHODS HANDLING AND STORING

8.2 FIRE GUIDANCE

8.3 EMERGENCY MEASURES

8.4 POSSIB. OF RENDERING SUBST. HARMLESS

8.5 WASTE MANAGEMENT

8.6 SIDE-EFFECTS DETECTION

8.7 SUBSTANCE REGISTERED AS DANGEROUS FOR GROUND WATER

8.8 REACTIVITY TOWARDS CONTAINER MATERIAL

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10.1 END POINT SUMMARY

10.2 HAZARD SUMMARY

10.3 RISK ASSESSMENT